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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,110	10/22/2001	Patrizia Caldirola	13425-052001 / 00382-US	5944

26161 7590 05/24/2005

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,110	CALDIROLA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,22-25,28-30,32-34,36-44,46-56 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *32* is/are allowed.

6)☒ Claim(s) *1-5,11-14,18,22-25,28-30,33,34,36-40,44,46-49,54,55,59 and 60* is/are rejected.

7)☒ Claim(s) *6-10,15-17,41-43,50-53,56 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2/03 3/0* TOM
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an RCE and to amendments filed on 2/14/05. Applicants have amended claims 2, 24, 25, 34, 36, 37, 44, 47, and 54-56. Applicant has canceled claims 27, 35, 57, and 58. There are fifty-one claims pending and fifty-one under consideration. Claims 1-18, 28-30, 32-34, 36-43, and 47-53 are compound claims. Claim 22, 23, 46, and 59-61 are composition claims. Claims 24, 25, 44, and 54-56 are use claims. This is the fourth action on the merits. Claim 32 was previously allowed. Objection was previously made to claims 6-10, 15-17, 41-43, 50-53, and 61. All other pending claims had been rejected. The application concerns some 1-sulfonylindole compounds, compositions, and uses thereof.

2. Applicants requested clarification of the status of claim 54. In the final rejection, claim 54 was rejected as obvious. In the advisory action claim 54 was also rejected as obvious but mistakenly listed as both rejected and objected to. It remains rejected as obvious in this action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous

Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/05 has been entered.

Response to Amendment

4. Applicants' limitation of the use claims to treatment of depression overcomes both the indefiniteness and the enablement rejections made to claims 24, 25, 34, and 44 of piperazine as a possible substituent R^4 overcomes the art rejections made in points #5 and #6 of the Final rejection.

Priority

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a) as follows: the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The Swedish application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-18, 22-30, 32-44, 46, and 47 of this application. The present claims are to molecules with 12 different heterocyclic radicals attached either to position 4, position 5, or both positions of an indole core.

Swedish Application 0003810-9 discloses indole compounds with only nine different heterocyclic radicals attached to the indole core. A benzyl group is a presently claimed R_6 substituent on these heterocyclic radicals. In the Swedish parent it is not.

6. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-18, 22-30, 32-44, 46, and 47 of this application. The contents of this provisional application appear identical to those of Swedish Application 0003810-9 discussed above.

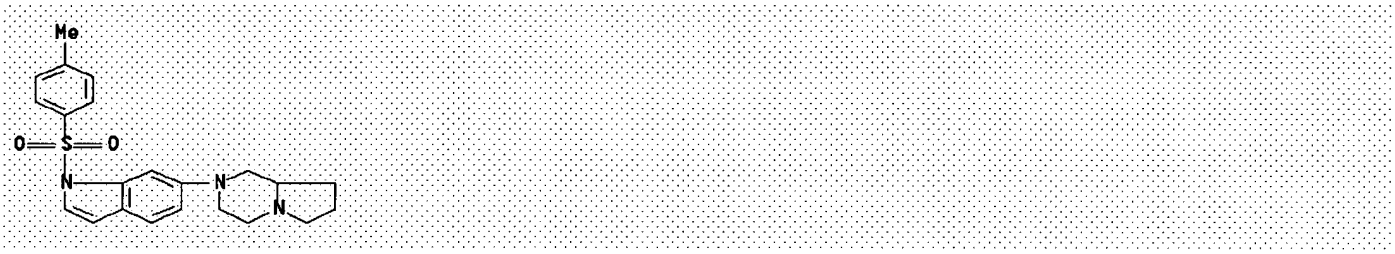
Thus, claims 1-18, 22-25, 32-34, 36-44, 46, and 47 have an effective filing date of 10/22/01. Claims 48-56 and 59-61 have an effective filing date of 10/20/00.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 11-14, 18, 22-25, 28-30, 33, 34, 36-40, 44, 46-49, 54, 55, 59, and 60 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD). The reference teaches the compound with registry number 299433-11-7 shown below. The Applicants claim



compounds with the hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical attached at either position 4 or position 5 of the indole core. The reference teaches a compound with hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical attached at position 6 of the indole core. The compound shown in the reference in Figure 1, page 1720 and is compound **4b**. A second relevant compound is **4a**. The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at positions 4 or 5 and the reference teaches attachment at position 6. These are ring position isomers. The compound of the prior art has the identical utility as that of the compound claimed by Applicants, namely as CNS therapeutic agent which binds to the 5-HT_6 receptor.

Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ullyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected

beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4–hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...".

Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-

azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* ($CONH_2$) and *ortho* (OCH_3) obvious over a dye with the same nucleus and *meta* ($CONH_2$) and *para* (OCH_3) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'–dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene).

Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other

positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) appeared in the 15 issue of Volume 10. A photocopy of the cover page of this issue is provided for Applicants convenience. Issue No. 15 has a publication date of 7 August 2000 and, in fact, was received by the USPTO library on Aug 1, 2000.

In the last sentence, first paragraph, second column, page 1720 Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) teaches that "specific concentrations of test compounds" were prepared. These presumably were in water, saline , or buffer and are compositions. Thus, Applicants claims 22 and 46 are made obvious. Binding data for the 5-HT_6 receptor are presented in Table 1, page 1720. Selectivity for the 5-HT_6 receptor for compound **4a** is presented in Table 2, page 1720. The expectation that compound **4a** is useful for treating

schizophrenia, depression, and memory dysfunction is taught in the final paragraph on page 1721. Thus, Applicants' claims 24, 44, and 46 are made obvious.

The synthesis taught by Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) is a coupling reaction, similar to that used by Applicants. Synthesis of the ring position isomers of the compounds of this reference requires only use of a ring position isomeric bromo-indole. Thus, the reference is an enabling disclosure for the synthesis of Applicants' claimed compounds.

Applicants' claim 18 lists the indolizidinyl species. The 5-aza-indolizinyl radical is Applicants' name for the hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical in the molecule pictured above.

The best evidence, which is absent in this application, would be a side by side comparison in Applicants' 5-HT_6 binding assay of the two compounds of Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) with the four position 4 and position 5 ring isomers, as claimed by Applicants. The PTO does not have the facilities to make such a comparison, yet Applicants have declined to provide such evidence. Of the cases discussed above, the case with the closest structural analog to the present compounds is *Ex parte Allais*, 152 USPQ 66. *Ex parte Allais*, 152 USPQ 66 involved positional isomers on the benzene portion of an indole compound, as does the present case. *Ex parte Allais*, 152 USPQ 66 involved an

animal assay drawn to reserpine-induced ptosis, presumably in the rat. The reserpine induced ptosis assay is a model of anti-depressant activity. Treatment of depression with Applicants' compounds is one of the pending claims and is an effect described in the prior art by the analogous compound. A four-fold difference in potency *in vivo* in *Ex parte Allais*, 152 USPQ 66 was not found sufficient to establish unexpected results.

Applicants make three arguments concerning this rejection. Firstly they argue that there are no *per se* rules of obviousness. Secondly they repeat their previous argument that there is no teaching within the reference to move the point of attachment of the hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical. Thirdly, they argue that structural similarity is not evidence of obviousness. Again none of these arguments are persuasive.

Concerning the first argument, rather than use the phrase *per se,* the Examiner now uses the similar phrase *prima facie.* According to the MPEP §2144.09, "[a] *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. " An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re*

Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979)". The cases of *Ex parte BIEL* 124 USPQ 109, *Ex parte Henkel* 130 USPQ 474, and *In re Grabiak* 226 USPQ 870 make clear the burden upon the Examiner to establish such a *prima facie* case with position isomers. In the present case, the compounds have both very close structures and identical utilities. Thus, the Examiner has met his burden.

Concerning the second argument that only one document has been used to make the obviousness rejection and that Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) contains no explicit direction to make Applicants' claimed position isomer. There is no requirement that two references must be used in every obviousness rejection. In fact, the Examiner has two form paragraphs available to him in writing such a rejection. One form paragraph is for the present single reference situation and the second is for the situation where a second reference is used to supply any claim limitation missing from the first reference. Every one of the thirteen cases, discussed above, bearing on ring position isomers in organic chemistry, used a single reference to make the *prima facie* case of obviousness. Both the MPEP §2144.09 and *In re Payne* 203 USPQ 245 at 254 make clear that the expectation of similar properties provides the direction to make close analogues of known compounds. Such is the situation here. *Ex parte Engelhardt*, 208 USPQ

343 at 349 shows that making position isomers is an art-recognized, "tool to obtain new and useful drugs". The MPEP §2144 states "[t]he rationale to modify ... the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law". In this case, the Examiner has used both common knowledge in the medicinal chemistry arts and legal precedent.

Concerning the third argument that close structural similarity alone is not sufficient to create a *prima facie* case of obviousness. At no time did the Examiner rely on the close structural similarity alone of the claimed and taught compounds as the only factor. The identical utility of the claimed and prior art compound and the routine nature of varying the position of attachment of substituents on core ring in the art of medicinal chemistry have always been the conclusive part of the evidence.

Allowable Subject Matter

8. Claim 32 remains allowed. Claims 6-10, 15-17, 41-43, 50-53,56, and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas McKenzie, Ph.D. whose telephone number is (571) 272-0670. After February 9, 2004, the Examiner may be reached

at (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James O. Wilson can be reached on (571) 272-0661. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK